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Graph-Based Approach for Spatial Heterogeneity Analysis in Tumor Microenvironment

B. Ben cheikh*[1], C. Bor-Angelier[2], D. Racoceanu[1]

[1]Sorbonne Universités, UPMC Univ Paris 06, CNRS, INSERM,, Laboratoire d'Imagerie Biomédicale (LIB), Paris, France, [2]Unicancer - Rhône Alpes Auvergne, Centre Jean Perrin - Service de Pathologie, Clermont Ferrand, France

Introduction/ Background

The interaction between tumor and surrounding microenvironment (TME) is recognized as playing an important role in the progression of the disease. Understanding of the interaction between tumor and immune system is the focus of several studies dedicated to the improvement of cancer immunotherapy effectiveness [1]. On the other hand, it has been shown that invasion and metastasis of breast tumors is influenced by collagen organization at the tumor-stromal interface [2]. The characterization of such interactions relies on an efficient spatial distribution quantification of TME. Graph-based analysis tools are the best suitable to answer this question as they have the ability to represent spatial arrangements and neighborhood relationships of different tissue components [3].

Aims

In this work, we propose a novel approach to characterize the spatial relationships between cancer cells and TME components in breast tumors, using graph theory and sparse sets' mathematical morphology (MM). The tools of morphology on graphs were first used in [4] to study the neighborhood relationships between cells in germinal centers from lymph nodes, then in [5] for semantic spatial configuration modeling in histopathology. In our study, we propose new morphological descriptors characterizing the tumor architecture and the interactions with TME cells.

Methods

Towards a better evaluation and understanding, we use simulated data of different breast tumor types <Figure1>, <Figure2>, where locations of cancer nuclei (CN), fibroblasts (synthesizers of collagen, FN), and lymphocytes (LN) are already known. In order to set neighborhood relationships between different cells, Delaunay graph [3] is first reconstructed on all cells, and alpha-shape filter [5] is applied to circumvent border effects, giving new graph denoted G <Figure 3.a>. The designed features are extracted basically from two different morphological operations. The first operation is composed of successive morphological erosions [4] applied to the subgraph induced by CN (denoted SGC, <Figure 3.a>), repeated until the subgraph is null. The curve given by the number of CN in terms of erosions provides 3 significant characteristics <Figure 3.d>: I) The origin slope describes the number of CN on the boundary of tumor aggregates (TA) and, thus, the tumor-stromal interface <Figure 3.b>; II) The area under curve (AUC) reflects the density within TAs, and III) the number of iterations outlines the morphologic radius of the largest TA and, consequently, the geodesic distance of the farthest tumor cell from LN and/or FN. The second morphological operation is composed of successive morphological dilations applied to SGC with non-overlapping control of labeled connected-components <Figure 3.c>. The goal behind this operation is to investigate the TME cells surrounding each TA. The ratio between the number of LN and the number of CN, and the means of the Euclidean and the geodesic distances of LN from CN on the boundary are calculated for each TA <Figure 3.e>.

Results

In this work, we have briefly presented a conceptual framework for analyzing the architecture of breast tumors and the interactions with the surrounding microenvironment. New graph-based features were proposed to characterize the spatial distribution of TME components and were tested on simulated data. In our

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future works, we will include adipose tissue [6], blood vessels and endothelial cells. We will also focus on the anisotropic characterization of collagen, and test the approach on real dataset.

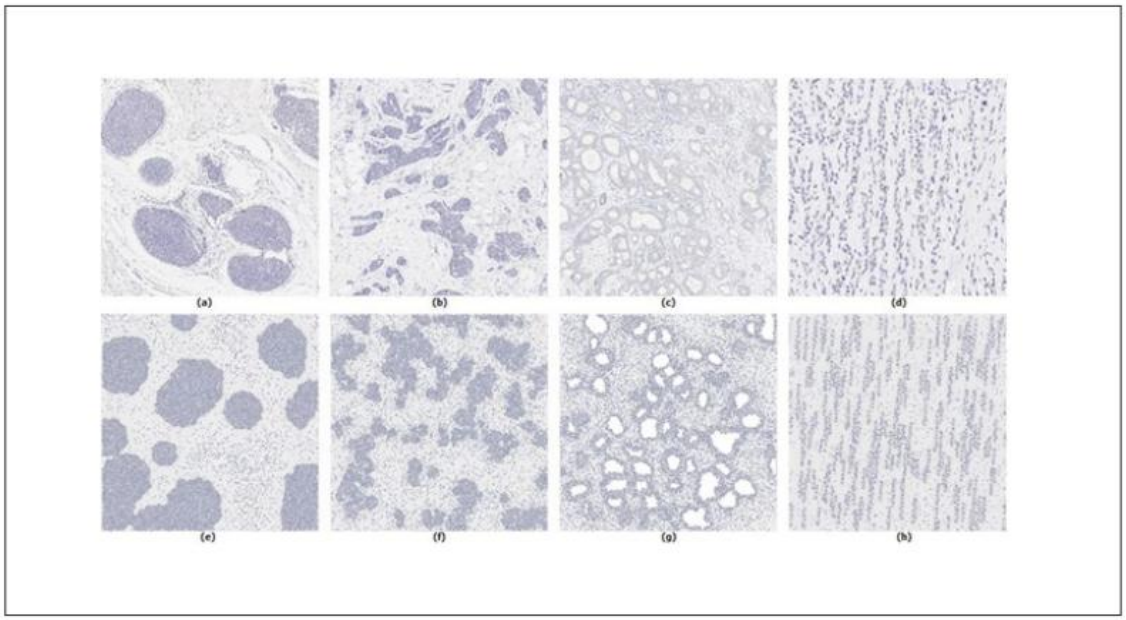

Figure 1: First row real data, second row simulated data. (a-e) Ductal Carcinoma in Situ, DCIS. (b-f) Invasive Ductal Carcinoma, IDC. (c-g) Tubular Carcinoma, TC. (d-h) Invasive Lobular Carcinoma, ILC (showing Indian File architecture).

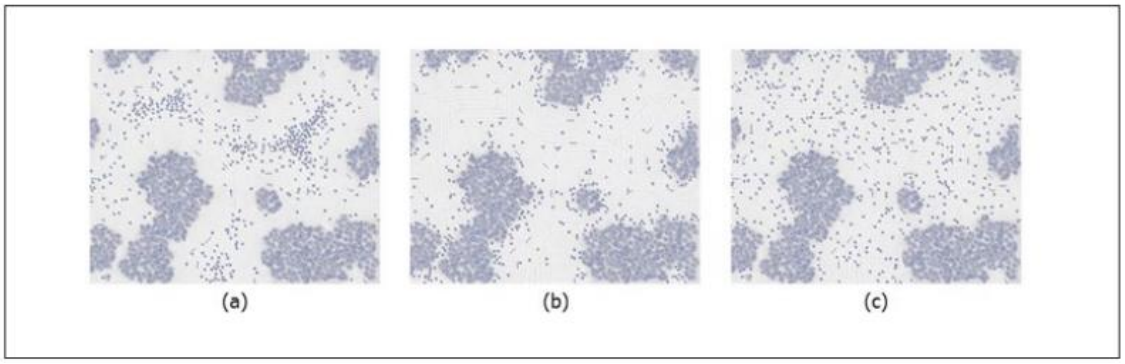

Figure 2: Simulated data of an IDC with lymphocytes in different spatial distributions. (a) Lymphocytes stood away from tumor aggregates. (b) Lymphocytes are surrounding the borders of tumor aggregates. (c) Lymphocytes are uniformly distributed.

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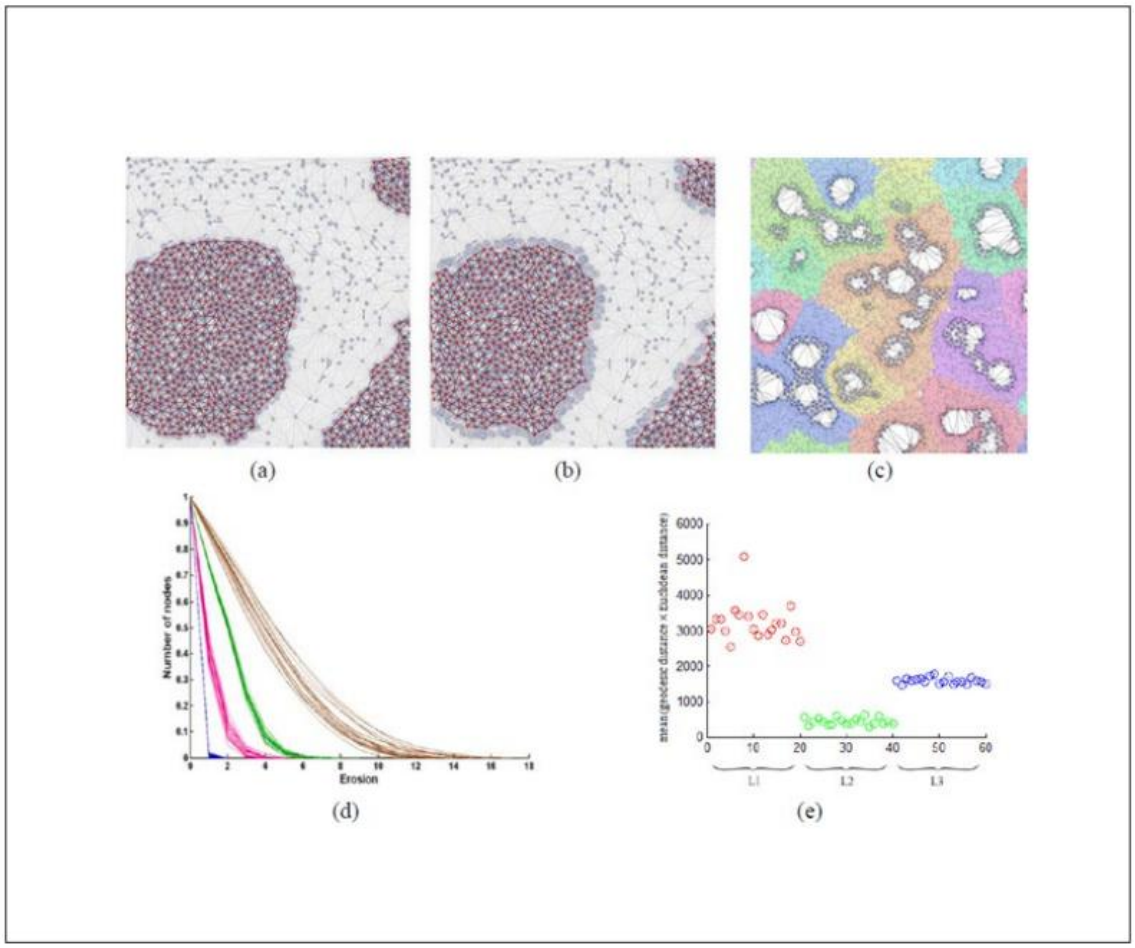

Figure 3: (a) SGC = (red nodes, black edges). (b) First erosion of SGC. (c) Variation of the number of CN in terms of erosion. (d) Labeled-dilation with non-overlapping control. (e) Mean distance of LN from TAs in the 3 different configurations shown in <Figure 2>.

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